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Relapse of Intracranial Germinoma 23 Years Postirradiation in a Patient Given Growth Hormone Replacement

Anne E. Kiltie, MA, MRCP(UK), FRCR,[1] Conor D. Collins, MRCP, FRCR,[2] H. Rao Gattamaneni, MD, FRCR,[1] and Stephen M. Shalet, FRCP[3]*

There is no clear evidence that growth hormone replacement therapy for treatment-related growth hormone deficiency in patients with childhood intracranial malignancies has a role in tumour relapse or second malignancy. A 16-year-old girl with an intracranial germinoma was treated with local radiotherapy, and subsequently received growth hormone replacement therapy as an adult. Three years after starting growth hormone therapy, 23 years after her radiotherapy treatment, the patient's tumour recurred. Surveillance requirements for patients receiving growth hormone in this setting are discussed. Med. Pediatr. Oncol. 29:41–44, 1997. © 1997 Wiley-Liss, Inc.

Key Words: cerebral tumour; germinoma; growth hormone replacement; radiotherapy; recurrence

INTRODUCTION

Intracranial germinomas are rare tumours which most frequently occur in 10- to 21-year-old patients [1]. They arise most commonly in the suprasellar and pineal regions, and therefore often present with endocrine dysfunction in addition to neurological dysfunction. Treatment with surgery and radiotherapy may exacerbate endocrine abnormalities and, following treatment, patients often require multiple hormone replacement therapy. Growth hormone is used to maximise growth potential in growth hormone-deficient children and is now being considered when they reach adulthood [2]. Concern has been expressed that growth hormone therapy might increase the risk of tumour recurrence, although to date there is no definite evidence. We report a patient who relapsed at 23 years from initial treatment, who was a recipient of growth hormone replacement therapy.

Case Report

In 1972, a 16-year-old girl presented with a 1-year history of episodic headache, visual field loss and a 6-month history of recurrent vomiting. She was found to have a left third nerve palsy and markedly reduced visual acuity bilaterally. Carotid angiograms demonstrated a suprasellar mass lesion. At craniotomy, there was a bulging mass in the sella, which emerged through the diaphragm and wrapped itself around the left optic nerve. Partial intracapsular removal was undertaken. Histology revealed a germinoma (atypical teratoma). Eighteen days postoperatively, she started a course of radical radiotherapy to the pituitary fossa, using a superior single unwedged field and two lateral parallel opposed wedged fields, all measuring 6 × 6 cm, to a dose of 4,250 cGy in 15 daily fractions, using an 8MV linear accelerator.

Endocrine assessment in November 1973 revealed growth hormone deficiency but the remainder of pituitary function appeared intact. The patient was commenced on sex steroid replacement therapy in 1975 following further endocrine assessment and pituitary function was again reviewed in 1981, and found to be unchanged.

The patient married in 1984 and as she wished to start a family, further endocrine assessment was undertaken in 1986. At that time, evidence of panhypopituitarism was present. Following the tests the patient complained of nausea, vomiting and dizziness. Once commenced on hydrocortisone and thyroxine replacement therapy, she developed diabetes insipidus, requiring desmopressin. At this time, a CT scan revealed an empty sella, and no recurrence of her tumour. Exogenous gonadotrophins were used in an attempt to induce ovulation, and follicular development occurred on several occasions, but no conception was achieved. Hence, the patient commenced sex steroid replacement therapy.

In 1992, she was entered into a trial of growth hormone replacement for adult growth hormone deficiency, and on growth hormone felt a great improvement in general well being, with less tiredness. Therefore, she continued on growth hormone at a dose of 2.0 IU daily (0.25

[1]Department of Clinical Oncology, [2]Department of Diagnostic Radiology, and [3]Department of Endocrinology, Christie Hospital NHS Trust, Manchester, United Kingdom.

*Correspondence to: S.M. Shalet, Department of Endocrinology, Christie Hospital NHS Trust, Wilmslow Road, Withington, Manchester M20 4BX, United Kingdom.

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Fig. 1. Sagittal MR scan (T1W sequence postcontrast) demonstrates presence of an enhancing tumour mass in suprasellar cistern in addition to tumour adherent to frontal horn of lateral ventricle.

units/kg/week) once the study was completed. Thus, she received growth hormone continually between 1992 and 1995 until tumour recurrence was diagnosed.

In early 1995, she complained of short-term memory loss and a CT scan revealed a mass above the pituitary fossa of relatively high density. Magnetic resonance imaging (Fig. 1) confirmed the presence of a suprasellar tumour, spreading widely to the hypothalamus, third ventricle, frontal lobe, thalamus, corpus callosum and pineal gland. There was no ventricular obstruction, meningeal involvement or spread below the foramen magnum. The alpha feta protein level was raised at 17 IU/l (normal <10), but the bHCG level was normal. A stereotactic biopsy of the tumour revealed a germinoma similar in histology to the original tumour.

The patient received three weekly JEB chemotherapy (carboplatin, etoposide, and bleomycin). Following six cycles of chemotherapy, after only a partial response, the patient received craniospinal irradiation, but died in February 1996 of septicaemia 2 months after radiotherapy.

DISCUSSION

Intracranial germinomas are rare tumours which occur most frequently in the second decade [1]. They are very radiosensitive, and have until recently often been treated with radical radiotherapy without biopsy, in view of their deep midline pineal and suprasellar locations. Only with the advent of stereotactic biopsy has histology routinely been available at the time of diagnosis. In more recently treated biopsied patients, event-free survival figures of 90–92% have been obtained using radiotherapy with or without chemotherapy [3].

Germinomas can metastasise widely throughout the Central Nervous System (CNS), but local recurrences also occur. Patients are often treated with craniospinal irradiation and a local radiotherapy boost to the tumour site, but local treatment alone has also been advocated [4,5]. Eleven years is the longest time to relapse, occurring within the radiotherapy field, and reported in a patient with a biopsy-proven germinoma of the pineal and suprasellar region treated with radiotherapy to the ventricular system and spine [6]. In reviewing 208 published cases, Fuller et al. [7] presented a freedom from relapse curve which purported to show a relapse from suprasellar germinoma at 17 years. However, reference to the original paper [8] demonstrates that the patient died at 17 years, there being no record of the time to relapse. Patients may have prolonged survival after relapse. One

TABLE I. Time Course for Endocrine Events and Scan Results

Date	Time since diagnosis	Endocrine status	Scan
1972	Presentation		Tumour
1973	1 year	GH[a] deficiency	
1975	3 years	GH and gonadotrophin deficiency	
1981	9 years	GH and gonadotrophin deficiency	
1986	14 years	ACTH[b], TSH[c], GH, and gonadotrophin deficiency, DI[d]	Empty sella, no tumour
1992	20 years	GH therapy started	(no scan)
1995	23 years		recurrence
1996	24 years	death	

[a]GH, growth hormone.
[b]ACTH, corticotrophin.
[c]TSH, thyroid stimulating hormone.
[d]DI, diabetes inspidus.

20-year-old patient who died of cerebrospinal metastases at 23 years from treatment, initially developed a local recurrence at 4 years, which was successfully retreated [9].

We therefore report a relapse at 23 years from treatment in a female patient treated with multiple hormone replacement therapy including growth hormone. This recurrence is later than any thus far described in the literature. This may in part demonstrate the strict follow-up of paediatric patients at the Christie Hospital. Patients are followed up indefinitely either annually or at 2 yearly intervals, in person if possible. Those who have moved out of the area continue on written follow-up in the majority of cases. As a result, recurrences are detected and documented which, in other centers with less stringent follow-up procedures, might have gone unrecorded.

Of concern, however, is the possibility that the administration of human growth hormone to this patient might have had a role in the development of the local recurrence, in view of the fact that growth hormone is mitogenic, and hence might activate malignant cell lines.

The time course for endocrine events and scan results for this patient is shown in Table I. Following radiotherapy to the hypothalamic pituitary axis to the dose prescribed in this case, growth hormone deficiency due to the treatment would be expected to manifest itself within 2 years in many cases. Corticotrophin (ACTH) and thyroid stimulating hormone (TSH) deficiencies usually present within the first 8 to 10 years. Radiotherapy has not been shown to cause diabetes insipidus. Thus, the development, in 1986 (14 years postradiotherapy), of ACTH and TSH deficiencies and the subsequent manifestation of diabetes insipidus following cortisol replacement suggests that there may have been tumour present at that time, too small to be detected on CT scanning. Subsequent growth of this tumour might have been stimulated by the growth hormone replacement therapy. Unfortunately, no CT scan was performed before initiation of growth hormone therapy as scanning might have revealed tumour at that time. Thus, the exact contribution of growth hormone replacement therapy to the growth in tumour size remains speculative. It is now our routine practice to perform a CT or MRI scan before the commencement of growth hormone therapy in all adult growth hormone-deficient patients with a history of tumour.

Human growth hormone is now widely used in paediatric oncology patients with radiation-induced growth hormone deficiency to maximise their growth. Although tumours arising from the hypothalamic-pituitary region may themselves cause growth hormone deficiency, any operation to remove them and subsequent radiotherapy may exacerbate that deficiency [10]. Radiotherapy is also used to treat tumours distant from the hypothalamic-pituitary region. The radiotherapy fields used may, however, include this region. For many paediatric brain tumours, whole head irradiation is included in the radiotherapy schedule and leads to growth hormone deficiency in a large proportion of patients [11]. In childhood acute leukaemia [12], cranial irradiation is used prophylactically, and craniospinal irradiation is used for CNS disease, at doses which can cause growth hormone (GH) deficiency. All such patients may potentially benefit from the use of growth hormone. As acute leukaemia and CNS tumours account for approximately 50% of all paediatric cancers, and as 50–60% of such patients now achieve long-term survival, a significant cohort of children treated for cancer may be candidates for growth hormone therapy.

Studies [13,14] have shown that administration of exogenous growth hormone increases the incidence of leukaemia and solid tumours in experimental animals. Studies looking at the effect of growth hormone on brain tumour recurrences in humans [15–18] have not shown any definite evidence of increasing rates of tumour recurrence. Ogilvy-Stuart et al. [18] looked at 207 patients with brain tumours, 47 of whom received growth hormone therapy. The relative risk of relapse if taking growth hormone was 0.82, but the 95% confidence intervals were wide at 0.28 to 2.37. Of 44 patients who had a CT scan before commencing growth hormone therapy, five patients relapsed, one of whom had residual tumour on the baseline scan, and one of whom had a low density non-enhancing lesion. Of the 39 who did not relapse, four had residual tumour on the baseline scan before commencing growth hormone, and there was no deterioration in appearance during the administration of growth hormone.

Concern has also been expressed that growth hormone therapy might cause leukaemia. Shalet [19] reviewed all the reported cases in 1993 and found no definite evidence for an association between growth hormone therapy and leukaemia, and no increase in the relapse rate from acute

lymphocytic leukaemia in those given growth hormone. Studies in acromegaly suggest an association between acromegaly and specific tumours, namely benign and malignant tumours of the colon [20]. However, these data cannot be extrapolated to the use of growth hormone replacement as, in acromegaly, growth hormone levels are supraphysiological and elevated for a prolonged period of time.

More recently, growth hormone has also been continued into adulthood in growth hormone-deficient patients. Many patients experience an improvement in their well being [2], and potential benefits include improvement in bone mineral density and body composition. As the survival figures for paediatric tumours slowly improve, increasing numbers of patients will receive growth hormone replacement, and for longer periods of time as more patients continue taking growth hormone into adulthood.

There is no definite evidence to incriminate growth hormone in the development of tumour recurrence or second malignancies in patients given growth hormone replacement therapy following treatment for childhood tumours. However, prolonged surveillance is required and clinicians should be vigilant to the possible role of exogenous growth hormone in relapse or induction of second tumours. It may be that growth hormone induces selected cancers only, as in the case of acromegaly. The ideal method for investigating any such role of growth hormone would be a large randomised controlled clinical trial. However, such an approach is probably untenable in view of the undoubted benefit gained from the administration of growth hormone by the large number of patients treated in this setting. If any relapses are caused by the use of growth hormone, the additional number is likely to be small. The setting up of a large national or international surveillance programme should hopefully clarify the situation. This programme would need to include all those receiving growth hormone compared with all those not receiving growth hormone within the same tumour groups. In all patients, whether in studies or surveillance programmes or not, computerised tomography or magnetic resonance imaging is required at the start of growth hormone replacement, in order to determine baseline appearances for comparison with later scans, to allow assessment of any tumour progression.

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